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A General Method for Asymmetric Arylation and Vinylation of Silyl Ketene Acetals

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A new biarylmonophosphine was developed for highly asymmetric arylation and vinylation of silyl enolates of acyclic esters with generality. The new stereocenters α to ester groups were formed in high enantiomeric excess. The method was applied to asymmetric synthesis of Profen drugs in a gram scale.

In method development of asymmetric α -arylation of carbonyl compounds, the main driving force is the need to prepare enantiopure Profens. Profens are a family of nonsteroidal anti-inflammatory drugs, including over-the-counter painkillers such as Ibuprofen, Naproxen, and Ketoprofen. They all contain the core structure of α -arylpropionic acids having tertiary stereocenters at α positions.¹ Profen enantiomers are known to possess significantly different pharmacological profiles. The (*S*) isomers are more biologically active than (*R*) forms. Consequently, Naproxen is sold solely in (*S*) form. Today, to access α -arylcarboxylic acids and derivatives, resolution² and asymmetric C-C couplings³ are common. Among them, direct asymmetric coupling between aryl electrophiles and enolates is one of the most efficient ways to access these compounds. In the past decade, a number of α -arylations of enolates have been developed to form quaternary centers in high *ee* (Fig 1a).⁴ The enolates were *in situ* generated from strong bases and carbonyl compounds including lactones,⁵ ketones,⁶ aldehydes⁷ and oxindoles.⁸ The use of strong bases prevented these methods from the construction of tertiary α -stereocenters, due to facile racemization of those products under basic conditions. Recently, we realized α -arylation of enolates in high *ee* which produced tertiary α -stereocenters. To prevent product racemization, silicon and tin enolates of esters,⁹ lactones¹⁰ and ketones¹¹ were used (Fig 1b). Other related metal-catalyzed methods were also reported. Examples include Cu-catalyzed coupling of diaryliodonium salts and soft enolates¹² and Ni-catalyzed coupling of α -bromoesters and aryl-metal reagents (Fig 1c).¹³

In our previously reported α -arylation of esters using chiral ligand **L4**, most aryl triflates carrying *para*-groups gave <90% *ee*.⁹ For example, the coupling of *p*-anisyl triflate and *t*-butyl propionate ended in 85% *ee* and the reaction stopped after partial conversion.

We decided to use the model coupling between *p*-anisyl triflate and a trimethylsilyl enolate derived from *t*-butyl propionate to seek a more stereoselective catalyst (Fig 2). Based on our past experience in arylation of ketones¹¹ and lactones,¹⁰ we hypothesized that the modification of *O*-benzyl side arm of ligand

L4 may help. Indeed monophosphines **L5** and **L7** carrying *m*-CF₃-benzyl groups led to 93% and 94% *ee*, respectively. Most other modification on the benzyl group led to inferior selectivity. In comparison, similar biarylphosphines on a 1,1'-binaphthyl backbone afforded only 30-64% *ee*.

Fig 1 Asymmetric C-C couplings to prepare α -arylesters and -aryllactones (structure of **L4**, see Fig 2).

Fig 2 Performance of chiral biarylphosphines in asymmetric coupling.

The choice of other reaction parameters was also crucial to good *ee*. (TMEDA)PdMe₂ was the optimal Pd source and Pd(OAc)₂ also gave good yield. LiOAc was essential to facilitate efficient enolate transfer. The ZnF₂ additive (0.2 equiv) can further accelerate the process. In terms of choice of solvents, good yield can also be obtained in toluene, benzene, *o*-xylene and diethyl ether. In PhCF₃, the model reaction of anisyl triflate was much slower and stopped after a partial conversion.

The Pd/L7 catalyst was successfully applied to many structurally diverse aryl triflates (Fig 3a). In almost all of cases ligand L7 was more stereoselective than ligand L4.⁹ Both electron-donating and electron-withdrawing groups can be present on the aryl rings. For an electron-neutral or electron-rich ArOTf, better *ee* was obtained in toluene than in PhCF₃. For an electron-poor ArOTf, however PhCF₃ was a better solvent. Notable, several alkenyl triflates also coupled well in toluene solvent. Silyl ketene acetals of *n*-butylate and valerate also coupled well (Fig 3b).

The Pd/L7 catalyst was successfully applied to asymmetric synthesis of some Profens including Fenoprofen, Flurbiprofen, Ketoprofen and Naproxen (Fig 4). In most cases, the coupling proceeded smoothly in >90% *ee*.¹⁴ The *t*-butyl esters of products can be easily hydrolyzed to release Profens using trifluoroacetic acid. After one crystallization the *ee* of synthetic Flurbiprofen was improved to 96% (84% yield) and after recrystallization, to 99%. The absolute configuration of synthetic Naproxen was determined to be (2*S*) by comparison with the reported optical rotation.¹⁵

Fig 3 Examples of aryl and vinyl triflates in asymmetric coupling of enolates.

Fig 4 Asymmetric synthesis of Profen esters.

In summary, we report herein a general Pd catalyst for asymmetric arylation and vinylation of ester enolates that formed tertiary carbon centers. The enantioselectivity was uniformly high as compared to our previous report in 2011.⁹ The method allows a quick access to many Profen analogues in >90% *ee* with a general scope. In our recent asymmetric arylations of cyclic ketones and lactones, weak CH...O hydrogen bonding was found to be responsible for asymmetric induction and the C-C reductive elimination was the stereo-determining step.¹⁰⁻¹¹ In the arylation of silyl enolates of acyclic esters, however it is probably transmetalation that dictates the stereochemical outcome, since (*E*) and (*Z*) isomers of a silyl ketene acetal gave significantly different *ee* values during arylation.⁹

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Notes and references

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